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IN- SITU NASAL GEL: MODERNISTIC ADVANCEMENT IN DRUG DELIVERY

Anil P. Palhal*[1], Girish S. Vispute[2], Piyush S. Mahajan[3], Dr. Surajj Sarode[4] and Dr. Shashikant Barhate[5]

Dept. of Pharmaceutics, Shree Sureshdada Jain Institute of Pharmaceutical Education and Research, Jamner (M.S), India.

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***Corresponding Author**
Anil P. Palhal
Dept. of Pharmaceutics,
Shree Sureshdada Jain
Institute of Pharmaceutical
Education and Research,
Jamner (M.S), India.

ABSTRACT

In-situ gel is a novel dosage form for nasal delivery of various drugs. It is instilled into the nasal cavity as low viscosity solution and then forms gel after coming in contact with the nasal mucosa. It also prolongs the contact time between drug and absorptive sites in the nasal cavity. In-situ nasal gel has got importance due to various advantages like rapid drug absorption, rapid onset of action, to avoid first pass metabolism and the drugs which are not suitable by other routes are given by nasal route. This review article contains various factors that influence nasal drug absorption like molecular weight, chemical form, polymorphism, solubility, dissolution rate, lipophilicity, pH, viscosity and osmolarity. Further, this review gives incite for the preparation of in-situ nasal gel by various methods viz., suspension polymerization, polymerization by irradiation, chemically and physically cross linked hydrogels etc. Evaluation of gels for gelation temperature, gelation time, appearance, pH, drug content, in vitro permeation studies, mucoadhesive strength, viscosity and rheological studies are also discussed.

KEYWORDS: In-Situ Nasal Gel, Mucoadhesive Drug Delivery System.

INTRODUCTION

Nasal drug delivery is an effective route of administration from the ancient days. There are many drugs which give better systemic availability through nasal route. Nasal therapy also called “Nasya Karma” has been recognized form of treatment in the Ayurvedic. System of Indian Medicine. Nowadays many drugs have better systemic bioavailability through nasal

route as compared to oral administration. The nasal delivery is a feasible alternative to oral or parenteral administration for some drug because of the high permeability of the nasal epithelium, rapid drug absorption across this membrane and avidance of first pass metabolism. Prolonged drug delivery can be achieved by various new dosage forms like in-situ gel. In-situ forming polymeric formulation are drug delivery system that is in sol form before administration in the body, but once administered, undergoes gelation in-situ to form a gel. In-situ nasal drug delivery system is the type of mucoadhesive drug delivery system.

Now a days in-situ gel has been used as vehicle for the drug delivery of the drug for both local treatment and systemic effect. In-situ nasal gel drug delivery system is advantageous over the conventional drug delivery system like sustained and prolonged release of drug, reduced frequency of administration, improved patient compliance and comfort. The in-situ gelation upon contact with nasal mucosa was conferred via the use of the thermo gelling Pluronic flake 127 whereas mucoadhesion and drug release enhancement were modulated via the use of Hydroxy Propyl Methyl Cellulose, Methyl Cellulose and polyethylene glycol respectively. The results revealed that the mucoadhesive polymer increased the gel viscosity but reduced its sol-gel transition temperatures and the drug release. The inclusion of polyethylene glycol polymer counteracted the effect of mucoadhesive polymer whereby it decreased the gel consistency and increased the sol-gel transition as well as in-vitro drug release. The in-vitro drug release performed through dialysis membrane and ex vivo studies performed by using sheep nasal mucosa. So this study points to the potential of mucoadhesive in-situ nasal gel in terms of ease of administration, accuracy of dosing, prolonged nasal residence and improved nasal bioavailability.

Intranasal drug delivery (mucoadhesive drug delivery system)

Traditionally, the medication for local diseases, such asrhinitis and nasal congestion, has not been administered through the nasal cavity. However, over the last few decades, intranasal (IN) delivery has been gaining much more attention as a promising route of drug administration for systemic therapy. Presently, it is being recognized for the delivery of therapeutic compounds including biopharmaceuticals, and for topical nasal treatments such as antihistamines and corticosteroids, and also for systemic delivery of analgesics, sedatives, hormones, vaccines and cardiovascular drugs by means of the nasal mucosa. This is because of the anatomy and physiology of the nasal passage, such as the highly vascularized epithelium, ready accessibility, large surface area, permeable endothelial membrane, high

total blood flow and the prevention of first-pass metabolism. IN administration is a "needleless" and non- invasive method of drug delivery through the nose to the brain and hence an alternative for systemic drug delivery.

Therapy through IN administration has been an accepted as a form of treatment in the ayurvedic system of Indian medicine and is called "Nasya Karma". Drug delivery through the nose is uncomplicated and convenient and can include the delivery of solutions, suspensions, powders, in situ gel and ointments. The avoidance of first pass metabolism, quick onset of action and lowered systemic exposure to drug are the main advantages of IN delivery. Nose-to-brain delivery of drug moieties are possible through the olfactory region, by neuronal and extracellular pathways located at the roof of the nasal cavity, whose neuroepithelium is the only part of the central nervous system (CNS) that is directly exposed to the external environment. The therapeutic agents are carried to the CNS through the olfactory neuroepithelium by the trigeminal nerve systems and olfactory nerve pathways. In both intravenous as well as oral administration, the blood-brain barrier (BBB) restricts the brain's access to the drug.

However, the intranasal route of delivery can also provide a route of entry to the brain that circumvents the BBB, because the olfactory receptor cells are in direct contact with the CNS Recently, the nasal mucosa has been examined as a possible route of administration to achieve a faster and higher level of drug absorption. The nasal cavity provides a number of distinctive benefits, such as ease of access, good permeability mainly for lipophilic and low molecular weight drugs, low proteolytic activity, prevention of harsh environmental conditions and hepatic fist pass metabolism, and potential direct delivery to the brain. Significantly, a number of invasive techniques in drug carrier systems, like the use of nanoparticles, liposomes, nanoemulsions, chemical modifi cations, the prodrug approach, and other invasive strategies like intra parenchymal, intraventricular and intrathecal delivery are used to increase the CNS-targeting of drugs. Large investigative studies have shown that when administered intranasally, vaccines can encourage both local and systemic immune responses.

Tables I and show the advantages and limitations of intranasal delivery along with their respective associated factors.

Table. 1: advantages (associated factors) of intranasal delivery).

Advantages	Factors
Improving patient Compliance.	Trained person not required • Needle-free (painless) • Non-invasive • User- friendly • Self-medication possible
Rapid absorption and onset of pharmacologic action. Good penetration Direct delivery of drug to CNS system	Highly vascularized mucosa Large mucosal surface area For lipophilic drugs For low molecular weight drugs Bypass BBB, via olfactory region Useful for local and systemic delivery
Avoids harsh Environment Low dose required	Less chemical and enzymatic Degradation. Avoids first pass metabolism • Avoids GIT degradation • Lower side effects • High bioavailability

NASAL ANATOMY AND PHYSIOLOGY

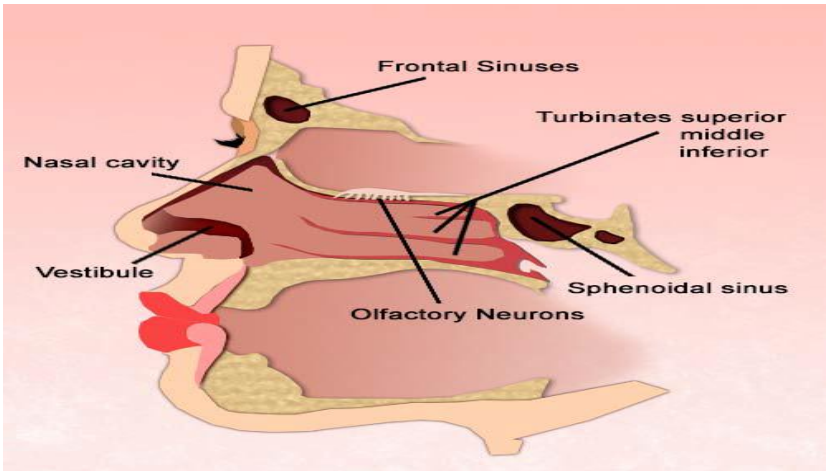


Figure 1: Anatomy of nasal cavity.

It is essential to have a clear understanding of anatomy and physiology of the nose and how it relates to the characteristics of the delivery system used.13 In humans and other animal species the major functions of the nasal cavity are breathing and olfaction. It also affords an important protective activity once it filters, heat and humidity the inhaled air before reaching the lowest airways.

The human nasal cavity has a total volume of 15-20ml and a total surface area of approximately 150cm2. Nose is divided into two nasal cavities via the septum. The volume of each cavity is about 7.5 ml and has a surface area around 75 cm2. pH of the mucosal

secretions ranges from 5.0 to 6.7 in children and 5.5 to 6.5 in adults. The nasal passage epithelium is covered by a mucus layer that is renewed every 10 to 15 min. The mucus moves through the nose at an approximate rate of 5 to 6 mm/min resulting in particle clearance within the nose every 20 min9 both symmetrical halves consist of four areas nasal vestibule, atrium, respiratory region and olfactory region.

Nasal Vestibule: Most anterior part of the nasal cavity is nasal vestibule, just inside the nostrils, and presents an area about 0.6 cm^2 this nasal portion is covered by a stratified squamous and keratinized epithelium with sebaceous glands is responsible for filtering out the air borne particles4,5 It is considered to be less important of the three regions with regard to drug absorption.

Atrium: Atrium is the intermediate area between nasal vestibule and respiratory region. Its anterior section is constituted by a stratified squamous epithelium and the posterior area by pseudostratified columnar cells presenting microvilli.

Respiratory Region

The nasal respiratory region is the largest part of the nasal cavity, also called conchae. The respiratory regionis the most important for systemic drug delivery. The respiratory epithelium is composed of four types of cells, namely, non-ciliated and ciliated columnar cells, basal cells and goblet cells. The respiratory region contains three nasal turbinates: superior, middle, and inferior which project from the lateral wall of each of the nasal cavity. The nasal respiratory mucosa, considered the most important section for delivering drugs systemically.

Olfactory Region

The olfactory region is located in the roof of the nasal cavity and extends a short way down the septum and lateral wall it is of about 10 cm2 in surface area and it plays a vital role in transportation of drugs to the brain and the CSF. When the drug is administered intranasally, it can enter into the brain via three different paths. The first one is the systemic pathway by which the drug is absorbed into the systemic circulation and subsequently reaches the brain by crossing BBB [especially lipophilic drug]. The others are the olfactory region and the trigeminal neural pathway by which drug is transported directly from the nasal cavity to CNS [cerebrospinal fluid and brain tissue]. There are different mechanism by which the drugs across the olfactory membrane to reach CNS. The first mechanism involves direct transfer of the drug to primary neurons of the olfactory epithelium and transport to the olfactory bulb by

intracellular axonal transport with subsequent possible distribution into more distant brain tissues. The second mechanism depends on the drug permeation across the olfactory susten tabular epithelial cells, either by transcellular or paracellular mechanisms followed by uptake into CNS. The last one employs pinocytosis by olfactory neurons.

Mucus membrane of nose and its composition

The nasal mucus layer is only 5 μm thick. Overall, nasal mucus layer consists of 95% of water, 2.5-3% of mucin, and 2% of electrolytes, proteins, lipids, enzymes, antibodies, sloughed epithelial cells and bacterial products.

Epithelial cells

The nostrils are covered by skin, the anterior one-third of the nasal cavity by a squamous and Transitional epithelium, the upper part of the cavity by an olfactory epithelium and the remaining portion by a typical airway epithelium which is ciliated, pseudostratified and columnar.

Basically there are two functions of these cells

1. Provide a physical barrier to the invasion of infectious microorganisms and allergic particles.
2. Work in conjunction with mucus glands and cilia to secrete and remove mucus and foreign particles from the nasal cavity.

Blood supply to nose

Nasal vasculature is richly supplied with blood to fulfil the basic functions of the nasal cavity such as heating and humidification, olfaction, mucociliary clearance and immunological functions. The capillary flow in the nasal mucosa was reported to be 0.5 ml/g/min.

ADVANTAGES OF NASAL DRUG DELIVERY

Rapid drug absorption Non-invasive Easy administration Good bioavailability Improved patient compliance and convenience. Large surface area for drug absorption**.** Rapid action. Less side effects The nasal drug is used when the drug which are not suitable for oral route. Crosses blood brain barrier. First pass metabolism is avoided.

DISADVANTAGES FOR NASAL DRUG DELIVERY

Removal of drug is not possible in nasal cavity. Less number of drugs are given by nasal route. Nasal irritant drugs are not given through this route.

Less than 25-200 µl volume of drugs given by this route. Lower molecular weight drugs are only given by this route. Frequently use of this route causes mucosal damage. The drug absorption may cause allergic problems. The reached amount of drug may vary in different regions (brain, spinal cord).

VARIOUS DOSAGE FORMS GIVEN BY NASAL ROUTE

Solution and Sprays: The drug solutions are nasally administered as nasal drops, sprays, and as metered dose nebulizer. The dose of the active ingredient administered depends upon the volume of drug and the concentration of drug in the formulation. The therapeutic levels of nitroglycerine, 3 mg/ml in central venous blood, 1.7 mg/ml in arterial blood and 0.4 mg/ml in peripheral venous blood were achieved within 2 minutes following intranasal administration of 0.8 mg/ml of nitroglycerine in normal saline. The effect of formulation variables such as dose of active ingredient, pH of the solution and its osmolarity on nasal absorption has been reported by various researchers.

Suspension: Suspensions for nasal administration are prepared by suspending the micronized drug in a liquid diluent or carrier suitable for application to the nasal mucosa. The preparation of suspension form gave a better insulin uptake and blood glucose reduction compared with that from the solution.

Powders: Powder dosage forms of drugs for nasal administration offer several advantages over liquid formulations. In the powder form, the chemical stability of the drug is increased, a preservative in the formulation is not required and it is possible to administer larger doses of drugs. Powder form is suitable for number of non-peptide drugs and is well suizted for peptide drugs. Polymer-based powder formulations show no adhesion until their absorption of mucus occurs on the nasal mucosa surface. This allows easy application to the nasal cavity by metered dose in sufflation even if the polymer is highly mucoadhesive. In addition, liquid preparations are more easily cleared to the nasopharynx and oropharynx from where they enter the posterior part of the tongue. Therefore, administration of nasal powders may increase patient compliance, especially if the smell and taste of the delivered drug is unacceptable. After getting in contact with the nasal mucosa, polymer-based powders are believed to form a viscous gel following absorbing water from the nasal mucus. Then, the free polymer chains penetrating into the tissue crevices can hold back the ciliary movement, which will increase the retention time of the drugs in the nasal cavity. Dry powder formulations can also avoid the utilization of preservatives and freeze storage, because they

do not support microbial growth and are more stable than solution. For these reasons, the dried powder is the most commonly studied formulation for the nasal drug delivery, including small hydrophobic drugs, peptide drugs and vaccine. prepared dry powder nasal influenza vaccine formulation by using spray-freeze-drying method; the results indicated that the powders were amorphous and more stable with respect to liquid formulations. In vivo experiments demonstrated that the powders significantly increased residence time in rats and elicit enhanced serum and mucosal antibody response.

Semi-solid dosage forms: A gel is a soft, solid or solid-like material consisting of two or more components, one of which is a liquid, present in substantial quantity. A gel should, on a time scale of seconds, not flow under the influence of its own weight. The solid like characteristics of gels can be defined in terms of two dynamic mechanical properties: An elastic modulus, G'(ù), which exhibits a pronounced plateau extending to time at least of the order of second; and a viscous modulus, G"(ù), which is considerably smaller than G'(ù). The first biological uses of gels (polymerized methyl methacrylate) were presented by the institute for Macromolecular Chemistry in Prague in 1960 and involved the manufacturing of contact lenses, arteries, etc.

Gelation occurs through the cross-linking of polymer chains, something that can be achieved by (i) covalent bond formation (chemical cross-linking) or (ii) non-covalent bond formation (physical crosslinking). Gels have been used for the delivery of drugs for both systemic and local actions. Many different methods using gels have been reported, including subcutaneous delivery for sustained release, buccal delivery, deliveries to the stomach, colon, rectum, vagina and nasal. Gel formulations with suitable rheological properties increase the contact time with the mucosa at the site of absorption. The increased contact time is caused by the mucoadhesive properties of the polymer in the gel and by the rheological properties of the formulation reducing the clearance by the nasal and ocular protective mechanisms.

VARIOUS APPROACHES OF IN-SITU GELATION

To cause sol to gel phase transition on the nasal surface the following type of systems are recognized.

1. pH Triggered system
2. Temperature dependent system
3. Ion activated system
4. Induced photo polymerization gelation (UV Induced gelation)

Ph triggered system: All the pH sensitive polymer contain acidic or basic groups that either accept or release proton in response to in environmental pH. In the case of anionic groups swelling of gel increases as the external pH increases, but decrease if polymer contains cationic groups.

Temperature dependent system: Temperature sensitive gels are classied into two type negatively thermo sensitive and second positively thermo sensitive. CST is critical solution temperature at which temperature gelation occurs.

1. Negatively thermo sensitive: Negative temperature sensitive gel had a lower critical solution temperature (LCST) and contract upon heating above the LCST.

2. Positively thermo sensitive: Positive temperature sensitive gel had an upper critical solution temperature (UCST).

Ion activated system: In situ formation is based on chemical reactions, following chemical reactions cause gelation, undergoes in situ gelling in the presence of mono- and divalent cations, including Ca, Mg, K and Na. Alginic acid undergoes gelation in presence of divalent/polyvalent cations.

Induced photo polymerization gelation

Photo polymerization is commonly used for in situ formation of biomaterials. A solution of monomers or reactive micromere and initiator can be injected into a tissue site and application of electromagnetic radiation used to form gel. The photo reaction provides rapid polymerization rate at physiological temperature. The photo polymerization systems when introduced to the desired site via injection get photo cured in situ with the help of beroptic cables and then release the drug for prolonged period of time.

MECHANISM OF DRUG ABSORPTION

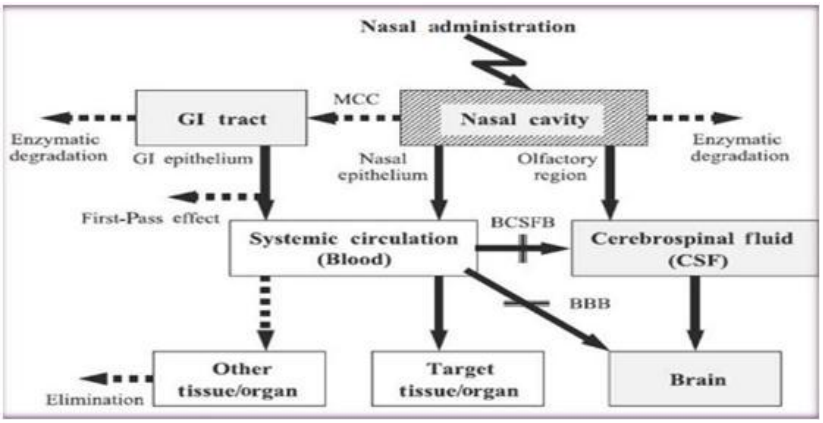
The fist step in the absorption of drug from the nasal cavity is passage through the mucus. Small, uncharged particles easily pass through this layer, though large or charged particles may find it more difficult to cross. The principle protein in the mucus is mucin, which has the potential to bind to solutes, hindering diffusion. Structural changes in the mucus layer are possible as a result of environmental changes (i.e. pH, temp é rature, etc.) subsequent to a drug' s passage through the mucus. Diff erent mechanisms for absorption through mucosa exist. They include transcellular (simple diffusion across the membrane) and paracellular

transport (movement between cell and transcytosis by vesicle carriers). Drug absorbed can potentially be metabolized before reaching the systemic circulation, and has limited residence time in the cavity Different mechanisms, such as passive diffusion (transcellular), passive diffusion (paracellular), carrier-mediated transport, transcytosis, absorption, and transport have been used for drug transport through the nasal epithelium.

Table. 2: discusses some important comparisons between the two mechanisms, which are widely used in drug transport through the nasal epithelium.

First mechanism (Paracellular process)	Second mechanism (Transcellular process)
• It has an aqueous route of transport. • The process occurs between the cell and transcytosis by vesicle carrier • This route is slow and passive • I t is suitable for hydrophilic drugs • There is an inverse log – log correlation between intranasal absorption and the molecular weight of water-soluble compounds • Poor bio-availability was observed for drugs with a molecular weight greater than 1000 Daltons	• It has a lipoidal route of transport • By an active transport route, drugs also cross cell membranes via carrier-mediated transport through the openings of tight junctions • It is a means of the transport of lipophilic drugs that show a rate-dependency on their lipophilicity • For example, chitosan, a natural biopolymer, opens tight junctions between epithelial cells to facilitate drug transport

Table. 3: mechanism of drug passage through the mucus.



APPLICATION OF IN-SITU NASAL GEL

1. An in-situ gel system for nasal delivery of mometasone furoate was developed and evaluated for its efficacy for the treatment of allergic rhinitis.

2.Gellan gum and xanthan gum were used as in situ gel forming polymers. Animal studies were conducted using an allergic rhinitis model and the effect of in situ gel on antigen induced nasal symptoms in sensitized rats was observed.

3.In-situ gel was found to inhibit the increase in nasal symptoms as compared to marketed formulation nasonex (mometasone furoate suspension 0.05%). Intact ciliated respiratory epithelium and normal goblet cell appearance indicated from histopathology of rat nasal cavity proved that these formulations were safe for nasal administration.

4.The formulation was in solution form at room temperature that transformed to a gel form when kept at 37o C. Animal experiments demonstrated hydrogel formulation to decrease the blood-glucose concentration by 40-50% of the initial values for 4-5 h after administration with no apparent cytotoxicity. Therefore, these types of systems are suitable for protein and peptide drug delivery through nasal route.

REFERENCES

1. Prabhjot Kaur, Tarun Garg, Goutam Rath & Amit K. Goyal A Rreview In situ nasal gel,Delivery Inpharma heathcare, 2015; 2-10.
2. Dey S. Mahanti B., Mazumder B., Malgope A., Dasgupta S. "Nasal drug delivery: An approach of drug delivery through nasal route", Der pharmaciasinica, 2011; 2(3): 94-106.
3. Anoop K.R., Nair S.C., John M.S., "In situ Gel: An Innovative Approach for Safe and Sustained Nasal Drug Delivery", International Journal of Pharmaceutical Sciences Review and Research, 2014; 24(1): 1-7.
4. Bajpai V. "In situ Gel Nasal Drug Delivery System – A Review", International Journal of Pharma Sciences, 2014; 4: 577-580.
5. Chavan P. Dhole S., Yadav M., "nasal drug delivery system: a review" world journal of pharmacy and pharmaceutical sciences, 2014; 3(12): 598-617.
6. Chien YW, Chang SF. In: Nasal Systemic Drug Delivery. New York: Dekker, 1989; 1-26.
7. Tortora GJ, Grabowski SR. Principles of Anatomy and Physiology. 17th ed. Harper Collins College Publishers, 2001.
8. Asane GS, Nirmal SA, Rasal KB, Naik AA, Mahadik MS, Madhusudan Rao YM. Polymers for mucoadhesive drug delivery system: A current status. Drug Dev Ind Pharm, 2008; 34: 1246-66.
9. Ahuja A, Khar RK, Ali J. Mucoadhesive drug delivery systems. Drug Dev Ind Pharm, 1997; 23: 489-515.

10. Arun Kumar Singh, Anita Singh, N.V. Stheeshmadhav, Nasal Cavity; A Promising Transmucosal Platform For Drug Delivery And Research Approach From Nasal To Brain Targeting, J. Drug delivery And T, 2012; 2(3): 22-23.
11. Suresh S, Bhaskaran S. Nasal drug Delivery: an overview. Ind J Pharm Sci., 2003; 65: 19-25.
12. L. Karpagavalli, B. Senthilnathan, A. Maheswaran and N. Narayanan A outbook on in situ mucoadhesive gel for nasal delivery IJPPR Human journal, 2015; 4(1): 113-128.
13. Robert O.Williams, David R.Taft, Jason T, Mcconville, Advanced Drug Formulation Design To Optimize Therapeutic Outcomes, 172: 281-301.
14. Swamy N G N, Abbas Z. Mucoadhesive in-situ gels as nasal drug delivery systems: an overview. Asian Journal of Pharmaceutical Sciences, 2012; 7(3): 168-180.
15. Kisan R. Jadhav, Manoj N. Gambhire, Ishaque M. Shaikh, Vilasrao J. Kadam, Sambaji S. Pisal, Nasal Drug Delivery System-Factor Affecting And Application, Current Drug Therapy, 2007; 2: 27-38.
16. Morath LP. Microspheres as nasal drug delivery systems. Adv Drug Delivery Rev. 1998; 29: 185–94.
17. Garg, T, Singh, O, Arora, S, Murthy, R. Dendrimer-A novel scaff old for drug delivery. Int J Pharm Sci Rev Res., 2011a; 7: 211-220.
18. Garg, T, Rath, G, Goyal, AK. Biomaterials-based nanofiber scaffold: targeted and controlled carrier for cell and drug delivery. J Drug Target, 2014c; 1-20.
19. P.R. Patil, S.S. Shaikh, K.J. Shivsharan, S.R. Shahi In situ gel: Anovel drug delivery system, Indo American journal, of pharma research, 2014; 4(1): 5409-5414.
20. Chandra Mohan Eaga et al, In-Situ Gels – A Novel Approach For Ocular Drug Delivery, Scholars Research Library Journal, 1: 21-33.
21. Sudipta Ganguly et al, A Novel in Situ Gel for Sustained Drug Delivery and Targeting, International Journal Of Pharmaceutics, 2004; 276: 83-92.
22. Banker and Rhodes, Drug and Pharmaceutical Science: Modern Pharmaceutics, Marcel Dekker, 2nd ed, 40: 568-594.
23. Nirmal H. B. et al, In-Situ Gel: New Trend in Controlled and Sustained Drug Delivery System, International Journal of Pharm Tech Research, 2010; 2: 1398-1408.